REMARKS

Upon entry of the present amendments, claims 6-11 constitute the pending claims in the present application. Claims 1-5 were previously cancelled. Claims 6-11 stand rejected.

Applicants have amended claim 6 to more clearly recite the subject matter of the claimed invention as being a "method of treating neurodegeneration in the central nervous system." Support for this amendment can be found throughout the original application, which describes methods of treating neurodegeneration in the central nervous system (CNS). This amendment adds no new matter. Applicants have similarly amended claim 10 to recite "wherein the neurodegeneration is associated with a neurodegenerative disease selected from..." This amendment merely corrects matters of form and adds no new matter.

Elections/Restrictions

In their February 10, 2009 response to the previous Office Action, Applicants argued that the claims all share the special technical feature of administering N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride to a patient having a neurodegenerative disease of the central nervous system, and therefore requested that the search and examination of the pending claims be expanded to encompass the full scope of the corresponding generic claims as per MPEP § 809.02(a) and 37 C.F.R. § 1.141(a). In the instant Action, the Examiner states that Applicants' argument is unpersuasive because "the species of neurodegenerative diseases of the central nervous system have differing special technical features including mechanisms and clinical effects."

Applicants wish to clarify that the methods of treating the indications recited in claim 10 all share the special technical feature of using N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride to treat neurodegeneration in the central nervous system through a common mechanism (i.e., regulation of the chaperone pathway); and each of the indications in claim 10 is a neurodegenerative disease of the central nervous system that can be treated in this fashion. The Office submits that the recited indications "have differing special technical features including mechanisms and clinical effects." Applicants respectfully point out that the recited indications will certainly differ from one another in one or more aspects

(otherwise they would be the same) but that unity of invention pursuant to the PCT only requires that the claimed embodiments share at least one special technical feature. Specifically, PCT Rule 13.2 provides:

> Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving *one or more* of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art (emphasis added).

Hence, as noted above, the methods of treating the indications in claim 10 all share the special technical feature of using the recited compound to treat neurodegeneration in the central nervous system, and thus unity of invention is satisfied when there is no prior art that discloses said special technical feature. The fact that the indications recited in the claimed methods may have other unshared properties is irrelevant for unity of invention purposes as long as the methods share at least one special technical feature. Accordingly, at least for this reason and in view of the remarks below addressing the instant obviousness rejection, Applicants submit that the full breadth of claim 10 satisfies the unity of invention standard and request examination of the full scope of the instant claims.

Claim Rejections – 35 U.S.C. § 103(a) – Claims 6-12

Claims 6-11 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kalmar et al. *Exp. Neurol.* 176, 87-97, 2002 ("Kalmar") in view of Bruening et al. *J. Neurochem.* 72, 694-699, 1999 ("Bruening"). The Examiner states that Kalmar teaches that "(+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (BRX-220) induces the expression of heat shock protein 70 and thus increases motor neuron and functional motor unit survival following axotomy-induced cell death in neonatal rats. Heat shock proteins, including hsp70, are further taught to provide cytoprotection of motor neurons." The Examiner further states that Bruening teaches that "up-regulation of hsp70 prolongs the survivability of motor neurons in an in vitro cell line ALS model." The Examiner alleges that it would have been *prima facie* obvious to "practice a method of treating a patient having ALS comprising administering BRX-220, since the compound was known to increase the expression

of hsp70, which was known [to] prolong the survivability of motor neurons in an ALS model." Applicants respectfully traverse the rejection.

The Examiner alleges that "BRX-220" as studied in Kalmar is the same as the claimed compound (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate. However, Kalmar does not identify BRX-220 in any way except by stating that it is "a potent analogue of Bimoclomol." *Nor did any reference in the art at the time of filing disclose the chemical identity of BRX-220.* Because one of skill in the art could not have known the identity of BRX-220 at the filing date of the instant application, there would have been no teaching or suggestion based on Kalmar or Bruening, either alone or in combination, to use (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or its citrate salt to treat a patient having CNS neurodegeneration in general, or for treating that which is associated with ALS in particular. For this reason alone, Kalmar and Bruening, taken either alone or in combination, fail to teach all of the elements of the pending claims.

Additionally, the Office submits that it would have been obvious to "use (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, since the chloride form would have been reasonably expected to have the same or substantially the same therapeutic benefit as the chloride citrate form." Apparently, the Office contends that Kalmar teaches the citrate form of (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride by reciting BRX-220. However, BRX-220 is not the citrate salt of this compound, which further demonstrates that one of skill in the art could not have envisioned the citrate salt, particularly when the structure of BRX-220 was unknown. Applicants respectfully point out that (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride is not a salt but rather a free base and that the "chloride" term refers to the covalent N-chloro substitution on the oxime, similar to how an "acid chloride" refers to the covalent bonded chloro substituent on a carbonyl carbon.

Further, even were the structure of BRX-220 to have been publicly available at the filing date (which it was not), the teachings of the combined references would not have motivated the skilled worker to make the claimed invention. Specifically, Bruening demonstrates

neuroprotection by genetic overexpression of HSP70 in primary motor neurons in a transgenic ALS mouse model (expressing mutant human SOD1 mutant protein). Kalmar, however, demonstrates that BRX-220 does *not* elevate HSP70 levels to any appreciable degree in motor neurons in the *in vivo* neonatal sciatic nerve crush model. Kalmar states "[f]ollowing neonatal nerve injury, there is ***little change*** in the intensity of hsp70 immunoreactivity within motorneurone cell bodies as can be seen in Fig. 3B at P7" (emphasis added) (see p. 91, left column). Kalmar comments that extensive astrogliosis takes place around injured motoneurones in the injured peripheral nerve model and thus looked to see whether increased HSP70 expression was associated with astrogliosis. Kalmar concludes that "the cells that upregulate HSP70 expression in the spinal cord in response to injury and treatment with BRX-220 are *astroglia*" and *not* motor neurons (emphasis added) (see p. 94).

For at least these reasons, neither Kalmar nor Bruening, alone or in combination, teach or suggest all the features of claim 6, and these references do not establish a *prima facie* case of obviousness for claims 6 or 7-11 which depend therefrom. Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the above remarks and amendments, Applicants submit that the pending application is in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at (212) 596-9000.

Applicants believe no fee beyond that required for the extension of time mentioned above is due with this response. However, if an additional fee is due, please charge our Deposit Account No. **06-1075**, under Order No. **004049-0018-101** from which the undersigned is authorized to draw.

Dated: October 8, 2009

Respectfully submitted,

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